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(54) TRANILAST-CONTAINING AQUEOUS PREPARATION FOR EXTERNAL USE

(57)Abstract:

PROBLEM TO BE SOLVED: To obtain a tranilast-containing aqueous preparation for external use having high safety, excellent absorbency of an active ingredient from an application site and good stability with slight irritation.

SOLUTION: This tranilast-containing aqueous preparation for external use is characterized in that an aqueous base is macrogols (polyethylene glycols) and a dissolution aid is further included in the preparation for external use obtained by including tranilast or its salt or a mixture thereof as an active ingredient in the aqueous base.

LEGAL STATUS

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* NOTICES *

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CLAIMS

[Claim(s)]
[Claim 1] Tranilast content aquosity external preparations which said aquosity bases are macro gall (polyethylene glycols), and are characterized by containing a solubilizing agent further in the external preparations make an aquosity basis come to contain by making tranilast, its salt, or those mixture into an active principle.
[Claim 2] Tranilast content aquosity external preparations according to claim 1 characterized by said solubilizing agents being the amines which have an alcoholic hydroxyl group.
[Claim 3] the amines which have said alcoholic hydroxyl group -- N-methyl glucamine, monoethanolamine, diethanolamine, triethanolamine, and fatty tuna -- the tranilast content aquosity external preparations according to claim 2 characterized by being one sort chosen from a meta-mall, diisopropanolamine, and tri-isopropanolamine, or two sorts or more.
[Claim 4] Said external preparations pH Tranilast content aquosity external preparations according to claim 1, 2, or 3 characterized by being about four to 8.5 range.
[Claim 5] Tranilast content aquosity external preparations according to claim 1, 2, 3, or 4 characterized by the concentration of the tranilast in said external preparations being about 0.05 to 30 mass %.
[Claim 6] Tranilast content aquosity external preparations according to claim 1, 2, 3, 4, or 5 with which said external preparations are characterized by being the liquid preparations chosen from suspension, an emulsion, liniments, lotions, and aerosols.
[Claim 7] Tranilast content aquosity external preparations according to claim 1, 2, 3, 4, or 5 with which said external preparations are characterized by being the half-solid-like pharmaceutical preparation chosen from plaster, an ointment, patches, pastes, cataplasms, and cream pharmaceuticals.
[Claim 8] Tranilast content aquosity external preparations according to claim 1, 2, 3, 4, or 5 with which said external preparations are characterized by being the solid-like pharmaceutical preparation chosen from a pessary agent and suppositories.
[Claim 9] Tranilast content aquosity external preparations characterized by being an anhydrous type and said aquosity bases being macro gall (polyethylene glycols) in the external preparations make an aquosity basis come to contain by making tranilast, its salt, or those mixture into an active principle.
[Claim 10] Tranilast content aquosity external preparations according to claim 9 characterized by said external preparations containing a solubilizing agent further.
[Claim 11] Tranilast content aquosity external preparations which said aquosity bases are low-grade polyalkylene glycols, and are characterized by containing a solubilizing agent further in the external preparations make an aquosity basis come to contain by making tranilast, its salt, or those mixture into an active principle.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention relates to the external preparations which make tranilast an active principle (active ingredient). It is related more with the external preparations which can be considered as the pharmaceutical preparation which is in the condition of having dissolved high-concentration tranilast in the basis, and was stabilized by using a specific compound for a detail as a basis. Furthermore, even if it does not use an absorption assistant, it excels in the absorptivity of the active principle in pharmaceutical preparation in the living body, and is related with little skin irritation and membrane stimulative external preparations.
[0002] In the case of cutaneous administration pharmaceutical preparation, the external preparations of this invention are effective in the therapy of allergic dermatitis (atopic dermatitis, cutaneous sensitization, etc.), keloid and a hypertrophic scar, eczema and a dermatitis group (keratodermia tylodes palmaris progressiva, lichen simplex chronicus Vidal, solar dermatitis, and perimeter [lips] dermatitis are included), an itch group (a hives Mr. lichen, straw FIRUSU, and fixed hives are included), Pruritus Cutaneous, a bug bite, psoriasis, palmoplantar pustulosis, etc.
[0003] Moreover, in the case of membrane application pharmaceutical preparation, it is effective in the therapy of the restenosis prevention after generalized allergic dermatitis besides the skin disease of the above-mentioned publication, bronchial asthma, a chlamydial infection, and percutaneous transluminal coronary angioplasty, a circulatory organ angiopathy, etc.
[0004]
[Background of the Invention] Tranilast is an antiallergic drug used as a therapy agent of various allergic diseases, and a keloid and a hypertrophic scar. It is examined by recent years as the preventive of the restenosis after percutaneous transluminal coronary angioplasty (PTCA), and a therapy agent of associated diseases. However, all had internal use agents in use, such as a capsule, a tablet, dry-syrups, and a fine grain agent.
[0005] It is known in pharmaceutics that the drug administered orally will receive the metabolic turnover which shifts to liver and is called a first-pass effect after being absorbed from an alimentary canal. Since metabolite does not reach to circulation blood in an effective original form at this time, from the field of a drug effect manifestation, it is invalid, and extent of bioavailability falls.
[0006] In order to maintain the drug concentration in effective blood, a lot of drugs will actually be prescribed for the patient, a burden may be given to a patient, and side effects, such as a stomach failure and a hepatopathy, may often be discovered. Development and research of pharmaceutical preparation other than [instead of an exception] an internal use agent are desired also for tranilast.
[0007] The medication method with which partial administration minded the route of administration which was excellent in pharmacokinetics and metabolism in the whole body disease in the partial disease as the application approach of drugs is useful on physic, and it is ideal that the burdens which demonstrate the drug effect greatest with a still smaller dose, and are given to a patient are few drugs.
[0008] And since a part is directly medicated with external preparations, such as an ointment and lotions, they can fully maintain the effective dose of the drug in the inside of the skin. Moreover, with the point which can mitigate the side effect accompanying internal use, it is thought that it is effective in the therapy of keloid and a hypertrophic scar, allergic dermatitis, etc.
[0009] Moreover, a thing avoidable [a stomach failure or the first-pass effect of liver] since it applies in the lower

rectum from CHUBU ENGINEERING CORPORATION in suppositories, A drug can shift among blood promptly by membrane absorption, and an operation can be made to continue continuously with gradual-release-izing, Compliance is improved, as for the merit on medicine, it is large that blood drug concentration is controllable, for administration to be easy also for a patient with still more difficult recipe of a child patient, a tablet, etc., etc., a systemic disease is begun, and it is possible to take effect also for diseases, such as a circulatory organ angiopathy.

[0010] However, since tranilast had the property very to be hard to melt into water, development of the pharmaceutical preparation in the condition of having made it dissolving in stability was difficult. As well-known reference about the external preparations of tranilast, there is [patches / external use] a precedence publication (JP,6-128153,A) etc. about a precedence publication (JP,4-99719,A, WO 97/28793) and an ointment.

[0011]

[Problem(s) to be Solved by the Invention] However, the external use patches in the above-mentioned publication have many fatty acid ester of an absorption assistant, and loadings of alcohols, and we are anxious about skin irritation. Moreover, since all have blended many water, dissolution stability is bad, and low-concentration pharmaceutical preparation-ization is a limit.

[0012] On the other hand, many water is included, and the tranilast which is an active principle does not dissolve into a basis in the ointment in the above-mentioned publication, but cutaneous-absorption nature is bad. And since the basic water solution is used as an absorption assistant, it is pH. It inclines toward the basicity side and there is a trouble that we are anxious about the skin irritation by the alkali.

[0013] It sets to this time and dissolution stability is bad acidity. pH The example of the tranilast external preparations which reported and realized pharmaceutical-preparation-izing in a field and high-concentration pharmaceutical preparation-ization which is excellent in the absorptivity in the living body using an aquosity basis does not exist until now.

[0014] This invention presents the gestalt of new external preparations, and its safety is high while it solves the trouble of said conventional technique towards utilization of the external preparations which make tranilast an active principle, and it excels in the absorptivity of the active principle from an application site extremely, and stability offers little stimulative tranilast content aquosity external preparations good.

[0015]

[Means for Solving the Problem] As a result of repeating research wholeheartedly, this invention persons discovered that compatibility was high to the macro gall (polyethylene glycols) whose tranilast is an aquosity basis, and got the tranilast content aquosity external preparations of the following configuration.

[0016] By making tranilast, its salt, or those mixture into an active principle, in the external preparations make an aquosity basis come to contain, said aquosity bases are macro gall (polyethylene glycols), and it is characterized by containing a solubilizing agent further.

[0017] the above-mentioned solubilizing agents are amines which have an alcoholic hydroxyl group -- desirable -- especially -- meglumine, monoethanolamine, diethanolamine, triethanolamine, and fatty tuna -- it is desirable to consider as one sort chosen from the group which consists of a meta-mall, diisopropanolamine, and tri-isopropanolamine, or two sorts or more.

[0018] Furthermore, pharmaceutical preparation based on the above-mentioned configuration pH It is about four to 8.5 range, and can be set as arbitration according to an application site.

[0019] And concentration of tranilast can be made into the range of about 0.05 to 30 mass % in the external preparations of this invention.

[0020] Moreover, by making tranilast, its salt, or those mixture into an active principle, in the external preparations make an aquosity basis come to contain, it is an anhydrous type and is characterized by using macro gall (polyethylene glycols) as an aquosity basis. If external preparations are an anhydrous type, even if it does not contain a special solubilizing agent, high-concentration tranilast may exist in an aquosity basis in the state of the dissolution. In addition, the solubilizing agent may be contained further.

[0021] In addition, as an aquosity basis, when low-grade polyalkylene glycols other than the above-mentioned macro gall (polyethylene glycols) are used, the same effectiveness as the case where macro gall is used can be expected.

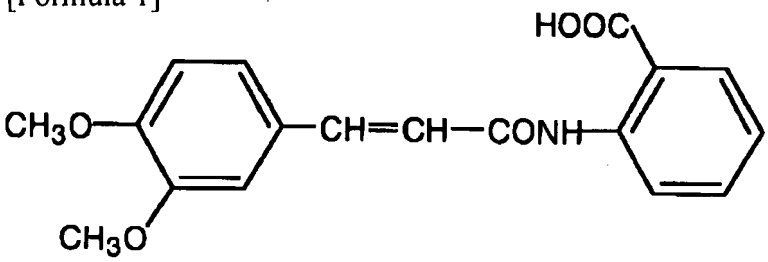
[0022]

[Detailed Description of the Means for Solving the Problem] The configuration of this invention is further explained to a detail. Especially"%" that shows loadings by the following explanation, unless it refuses, "mass %" is meant.

[0023] this invention persons were able to complete the tranilast aquosity external preparations which were extremely excellent in skin permeability, as a result of repeating examination wholeheartedly that the pharmaceutical preparation which is stability for a long period of time should be completed in the form which tranilast dissolved into the aquosity basis.
[0024] The tranilast content aquosity external preparations of this invention make it a basic feature to have used macro gall (polyethylene glycols) as an aquosity basis in the external preparations make an aquosity basis come to contain by making tranilast, its salt, or those mixture into an active principle.
[0025] In order to dissolve the tranilast which originally hardly dissolves in water in stability as aquosity pharmaceutical preparation, macro gall with high tranilast and compatibility (polyethylene glycols) was used as a basis.

[0026] As an example of macro gall (polyethylene glycols), the macro gall 200, the macro gall 300, macrogol 400, the macro gall 600, the macro gall 1000, macrogol 1500, the macro gall 1540, the macro gall 2000, macrogol 4000, macrogol 6000, etc. can be illustrated. In addition, the figure which continues after macro gall means the average molecular weight of macro gall (polyethylene glycols).
[0027] The above-mentioned macro gall (polyethylene glycols) is solids-like in low molecular weight (about 600 or less) at the molecular weight (about 600-2000) of whenever [liquid and middle] in the shape of a half-solid, and the amount of macromolecules (about 2000 or more). Therefore, it becomes possible to adjust the description of external preparations with the shape of the shape of liquid and a half-solid, and a solid by adjusting the molecular weight of the macro gall (polyethylene glycols) which are a basis.
[0028] In addition, macro gall is known as most typical thing of an aquosity basis, and adoption of the macrogol ointment is carried out to the Japanese pharmacopoeia. Like the above, that from which molecular weight differs can be blended with arbitration, respectively, and aquosity liquids and solutions, an ointment of a half-solid, solid suppositories, etc. of a solution mold can be manufactured by adjusting hardness.
[0029] As aquosity liquids and solutions of a solution mold, suspension, an emulsion, liniments, lotions, aerosols, etc. can be illustrated, for example. In addition, they are liniments (Liniments) here. They are liquefied or the thing of the external preparations rubbed in and used for the skin which **(ed) in the shape of mud usually. Moreover, as half-solid-like pharmaceutical preparation, plaster, an ointment, patches, pastes, cataplasms, cream pharmaceuticals, etc. can be illustrated. Moreover, a pessary agent, suppositories, etc. can be illustrated as solid-like pharmaceutical preparation. These can be prepared by adding various additives with a conventional method.
[0030] And in pharmaceutical preparation, by using a specific solubilizing agent, it dissolves, even if tranilast is the high concentration around 30%, and existence becomes possible by the stable state. Moreover, if pharmaceutical preparation is an anhydrous type even if it does not use a solubilizing agent etc. for a surprising thing separately, tranilast will dissolve to the concentration around 3%, and the existence of it will be attained by the stable state. In other words, if it is in pharmaceutical preparation with few contents of tranilast, even if it omits combination of a solubilizing agent, the dissolution to a basis of tranilast is attained.
[0031] When one sort chosen from the group of the amines which have an alcoholic hydroxyl group as the above-mentioned solubilizing agent, or two sorts or more are used, the soluble improvement to a basis becomes remarkable and is desirable.
[0032] as the amines which have the above-mentioned alcoholic hydroxyl group -- N-methyl glucamine (meglumine, chemical name:1-methylamino-1-deoxy-D-glycitol), diisopropanolamine, tri-isopropanolamine, and fatty tuna -- it is desirable from the group of a meta-mall (tris (hydroxymethyl) aminomethane), monoethanolamine, diethanolamine, and triethanolamine independent or to use it, choosing two or more sorts.
[0033] Although it changes with the class of solubilizing agent to be used, and use gestalten (anhydrous and the Arimizu type, or liquefied, a half solid, a solid, etc.) of pharmaceutical preparation, when diisopropanolamine is used as a solubilizing agent for example, if the content in the external preparations of the above-mentioned solubilizing agent is about 10% or less, it is enough.
[0034] In addition, the tranilast used as an active ingredient of the external preparations shown by this invention can be used also as the salt or those mixture also as a free object. And the content of tranilast can be suitably chosen according to the disease to apply. Usually, the content of tranilast becomes remarkable [more ones / effectiveness]. this invention -- the former -- high concentration -- the dissolution into a basis is possible till around about 30%, for example, it is about 0.1 - 20% of range desirably about 0.05 to 30% in cutaneous administration pharmaceutical preparation, and can

specifically be preferably used in about 5 - 20% of range about 1 to 30% in the viewpoint of the blood-flow translatability to the whole body with membrane application pharmaceutical preparation.
[0035] Moreover, since external preparations of this invention are characterized by consisting of an aquosity basis, they can blend water, alcohols, a surfactant, etc. freely. In addition, it became possible to eliminate the water in the conventionally indispensable basis in this invention. Therefore, even if it becomes unnecessary to have taken into consideration the effect of the water in the field of the dissolution stability of tranilast, and shelf life and did not use a stabilizing agent etc., the mothball of pharmaceutical preparation became possible.
[0036] In addition, in manufacturing the external preparations of this invention, according to an application site, the excipient used for preparation of the usual external preparations can be used, choosing it suitably. For example, they are a surfactant, a stabilizing agent, antiseptics, an anti-oxidant, a solvent, and pH suitably by request. A modifier, absorption enhancers, an ultraviolet ray absorbent, an aromatic, a coloring agent, and other additives can be combined.
[0037] In addition, the tranilast used as an active ingredient by this invention is an N-(3, 4-dimethoxy cinnamoyl) anthranilic acid shown by the degree type.
[0038]
[Formula 1]



As for the external preparations of this invention, tranilast may exist in the state of the dissolution in a basis under acidity with the low stability of tranilast by the above-mentioned configuration. Therefore, pH The selection range of a field became large as compared with the conventional tranilast external preparations. For example, weak acidic field with little [excelling at cutaneous-absorption nature in the case of skin external preparations, such as lotions and an ointment,] skin irritation pH About four to 7 range is desirable. Moreover, neutral region with little [in the case of membrane absorbents, such as suppositories,] membrane stimulative pH About seven to 8.5 range is desirable.
[0039] Generally these combination component is recognized as medical-application external preparations, and is used widely, the macro gall and the alcoholic amines which are shown by this invention are excellent in the solubility of a drug, safety is high and a feeling of use excels [manufacture / to simple and homogeneity / it / it is good and] in the field of practicality.
[0040] In addition, as an aquosity basis, when low-grade (four or less C) polyalkylene glycols other than the above-mentioned macro gall (polyethylene glycols) are used together or independent used, the same effectiveness as the case where macro gall is used can be expected. As a low-grade polyalkylene glycol, a polypropylene glycol, a polybutylene glycol, etc. can be illustrated, for example.
[0041]
[Effect of the Invention] By the above-mentioned configuration, the tranilast content aquosity external preparations of this invention had high safety, and were extremely excellent in the absorptivity of the active principle from an application site, and stability was able to consider them as little stimulative pharmaceutical preparation good.
[0042]
[Example] Next, the example which checks the effectiveness of this invention and which went to accumulate is explained concretely. In addition, unless it is not limited to the range of an example and deviates from the summary of this invention, various design changes are possible for this invention.
[0043] The external preparations of each formula shown in the <example> table 1 were prepared according to the approach generally used, respectively with a liquid and half-solid and solid external preparations.
[0044] About the formula (example 3 in JP,6-128153,A) shown in Table 1 which blended the basis of a <example of comparison> hydrophilic property, it prepared among this official report according to the approach of a publication in the example 3.
[0045]

[Table 1]

(単位：wt%)

	比較例	実－1	実－2	実－3	実－4	実－5	実－6	実－7	実－8	実－9	実－10	実－11
	半固形	液 状	液 状	液 状	液 状	液 状	半固形	半固形	固 形	半固形	半固形	液 状
<活性成分>												
トラニラスト	10	3	5	5	5	10	10	20	20	5	10	10
<塩基性水溶液>												
1% $NaHCO_3$ aq	40	—	—	—	—	—	—	—	—	—	—	—
<溶解補助剤>												
ジイソプロパノールアミン	—	—	2	1.8	1.6	4.48	4.48	8.95	8.95	2.24	4.48	4.48
<親水基剤>												
親水軟膏	50	—	—	—	—	—	—	—	—	—	—	—
マクロゴール 200	—	92.45	88.45	88.65	88.85	80.52	—	—	—	—	—	—
マクロゴール 400	—	—	—	—	—	—	43.52	29.05	9.05	45.71	43.47	50.12
マクロゴール1500	—	—	—	—	—	—	17	17	17	17	17	—
マクロゴール4000	—	—	—	—	—	—	20	20	44	25	20	—
<界面活性剤>												
ポリオキシエチレン硬化ヒマシ油60	—	—	—	—	—	—	—	—	—	—	—	5.4
<H_2O>	—	—	—	—	—	—	—	—	—	—	—	30
<安定化剤>												
ジブチルヒドロキシトルエン	—	0.5	0.5	0.5	0.5	1	1	1	1	1	1	—
ベンジルアルコール	—	4	4	4	4	4	4	4	—	4	4	—
無水クエン酸	—	0.05	0.05	0.05	0.05	—	—	—	—	0.05	0.05	—
pH	6.56	4.30	5.76	5.93	5.84	7.75	7.74	7.76	7.79	5.74	6.81	7.33

[0046] A. The stability test was performed about the pharmaceutical preparation for which the formation of stability test pharmaceutical preparation of pharmaceutical preparation was possible.
[0047] 1) The following marketing raw material was used for preparation of the raw material test pharmaceutical preparation used for test pharmaceutical preparation. Tranilast, diisopropanolamine, the macro gall 200, macrogol 400, macrogol 1500, macrogol 4000, polyoxyethylene hydrogenated castor oil 60, benzyl alcohol, anhydrous citric acid, dibutylhydroxytoluene [0048] 2) The test pharmaceutical preparation of each example which carried out preservation condition preparation was saved under the temperature of the following conditions, and a humidity ambient atmosphere.
** temperature condition: -- 40 degree C and 75%RH use device: -- Tabai Espec soundness test machine CSH-210** temperature condition: -- 5-degree-C use device: -- SANYO incubator MIR-253** temperature condition: -25-degree-C use device: -- SANYO MEDIKURU MPR-411 -- F [0049] 3) the test pharmaceutical preparation of each example saved on a trial item and the test-method above-mentioned conditions -- with time -- examining -- description -- appearance observation and pH And content measurement was performed. In addition, pH It measured about the liquid diluted with water, and content measurement was measured with HPLC assay.
Use device: Horiba pH Meter F-23 island body fluid object chromatograph equipment LC-10A [0050] A test result is as being shown in Table 2-3-4-5-6. Each of each formula pharmaceutical preparation shown in the example was very stable, without starting aging.
[0051]
[Table 2]

5℃低温保存安定性（性状外観）

	実施例5	実施例7	実施例8	実施例9	実施例10	実施例11
調製直後	微黄色澄明	微黄白色	微黄白色	微黄白色	微黄白色	淡黄色澄明
保存1ヶ月後	微黄色澄明	微黄白色	微黄白色	微黄白色	微黄白色	淡黄色澄明
保存3ヶ月後	微黄色澄明	微黄白色	微黄白色	微黄白色	微黄白色	淡黄色澄明

[0052]
[Table 3]

－２５℃低温保存安定性（性状外観）

	実施例１	実施例２	実施例３	実施例４
調製直後	微黄色澄明	微黄色澄明	微黄色澄明	微黄色澄明
保存1ヶ月後	微黄色澄明	微黄色澄明	微黄色澄明	微黄色澄明
保存3ヶ月後	微黄色澄明	微黄色澄明	微黄色澄明	微黄色澄明

[0053]
[Table 4]
４０℃・７５％ＲＨ（性状外観）

	実施例５	実施例７	実施例８
調製直後	微黄色澄明	微黄白色	微黄白色
保存1ヶ月後	微黄色澄明	微黄白色	微黄白色
保存3ヶ月後	微黄色澄明	微黄白色	微黄白色

[0054]
[Table 5]
４０℃・７５％ＲＨ（ｐＨ）

	実施例５	実施例７	実施例８
調製直後	７．７５	７．７６	７．７９
保存1ヶ月後	７．７４	７．７５	７．７８
保存3ヶ月後	７．７１	７．７３	７．７０

[0055]
[Table 6]
４０℃・７５％ＲＨ（残存率％）

	実施例５	実施例７	実施例８
調製直後	１００．０	１００．０	１００．０
保存1ヶ月後	１００．２	１００．３	１００．８
保存3ヶ月後	９９．８	１００．１	９９．７

[0056] B. It carried out by the following approach about 10% liquid preparations (example 5) which used for contrast pharmaceutical preparation the example of a comparison which contains skin translucency test tranilast 10%, and prepared it like the case of a stability test by the above, and 10% semisolid preparation (example 6).
[0057] 1) The radiographic examination approach : an artificial skin (Alloask) is fixed to the Francis mold diffusion cel, keep temperature at 37 degrees C, set under a protection-from-light condition, and it is the inside of a test tube (inch vitro). The transparency experiment was conducted. the cel volume by the side of a receiver -- 20cm3 and effective diffusion surface area -- 3.8cm2 it was .
[0058] The physiological saline was filled to the receiver side of a cel, and the skin was installed so that the dermis side of the skin might touch a physiological saline. 100mg of pharmaceutical preparation was applied to the horny layer side, and this time was made into time amount zero. 1mL sampling was carried out from the receiver side for every (at a total of five times 2**4**6**8**24 hours after) fixed time amount, and the quantum of the amount of tranilast in a physiological saline was carried out by HPLC. Physiological saline 1mL which does not newly contain a drug was added to the receiver side of a cel after the sampling. The translucency test calculated the average repeatedly by a unit of 6 times altogether.
[0059] 2) A test result and an evaluation test result are as being shown in drawing 1 . Although the tranilast

concentration which blends any pharmaceutical preparation was the same, to the ointment pharmaceutical preparation of the example of a comparison, the liquid preparations of an example 5 and the semisolid preparation of an example 6 showed surprising marked permeability, and having the extremely excellent cutaneous-absorption nature was suggested.

[0060] C. It carried out depilating mechanically by rabbit skin continuation stimulus sex-test 1 ********** hair clipper, and did not have an island skin, but four spreading parts of 3-4cm around were prepared behind the white rabbit which checked that the regions-of-back skin was macroscopically normal, and the continuation spreading trial for 1 or 5 times, and a total of 14 days was carried out for the test pharmaceutical preparation of a formula shown in the examples 5 and 6 on the 1st. In order to prevent for contrast that a rabbit licks a spreading part, using those bases, it was made to equip with the collar for **** prevention.

A rabbit:Japan native species, an one white male [/day] (weight: 2.5-3.0kg) spreading trial, and a day 5 times [/] spreading trials: A total of four birds [0061] 2) About the indication of the erythema and scab in observation of an administration part, the evaluation approach administration part, and its perimeter, an edema, and desquamation, it observed before administration every day and evaluated in accordance with the criteria shown in Table 7. Moreover, about each test pharmaceutical preparation, the evaluating point per animal (what **(ed) the sum total of all scores by the number of use animals and judgment days) was searched for, and stimulative reinforcement was judged in accordance with the criteria shown in Table 8.

[0062] 3) The result of observation, measurement result observation, and measurement is shown in Table 9. examples 5 and 6 showed -- each of liquefied and semisolid preparation has got used well with the skin front face, change did not arise at all to an administration part, and skin irritation was not accepted at all in the continuation spreading trial. In addition, the general status of a rabbit was normal through the duration of test satisfactory.

[0063]

[Table 7]

皮膚連続刺激性の判定基準

判定項目	皮膚反応の程度	評点
紅斑及び痂皮	紅斑なし	: 0
	わずかな紅斑	: 1
	明らかな紅斑	: 2
	強い紅斑	: 3
	強い紅斑に痂皮形成	: 4
浮腫	浮腫なし	: 0
	わずかな浮腫	: 1
	明らかな浮腫	: 2
	著しい浮腫	: 3
落屑	落屑なし	: 0
	わずかな落屑	: 1
	明らかな落屑	: 2
	著しい落屑	: 3

[0064]

[Table 8]

皮膚連続刺激性の評価基準

評価点	評価基準
0	Non-irritant
0.1 ～ 2.0	Slightly irritant
2.1 ～ 4.0	Moderately irritant
4.1 ～10.0	Severely irritant

[0065]

[Table 9]

観察及び測定結果

観察時期	観察項目	群	1回／日投与								5回／日投与							
			実施例5				実施例6				実施例5				実施例6			
		試験番号	A1		A2		B1		B2		A1		A2		B1		B2	
		投与部位	a	b	a	b	a	b	a	b	c	d	c	d	c	d	c	d
1日後	紅斑・痂皮		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	浮腫		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	落屑		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5日後	紅斑・痂皮		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	浮腫		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	落屑		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10日後	紅斑・痂皮		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	浮腫		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	落屑		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
14日後	紅斑・痂皮		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	浮腫		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	落屑		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
評価点	基剤		0				0				0				0			
	薬剤		0				0				0				0			
判定	基剤		Non-irritant				Non-irritant				Non-irritant				Non-irritant			
	薬剤		Non-irritant				Non-irritant				Non-irritant				Non-irritant			

[Translation done.]